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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/922,958	08/07/2001	Lorenz Poellinger	3743/49008	9818

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WIGGIN AND DANA LLP
ATTENTION: PATENT DOCKETING
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EXAMINER	
FETTEROLF, BRANDON J	
ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/922,958	POELLINGER ET AL.	
	Examiner	Art Unit	
	BRANDON J. FETTEROLF	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 December 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33,35 and 36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33, 35 and 36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to the Amendment

The Amendment filed on 12/26/2007 in response to the previous Non-Final Office Action (6/27/2007) is acknowledged and has been entered.

Claims 33 and 35-36 are currently pending and under consideration.

Rejections Withdrawn:

The rejection of Claims 33 and 35-36 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, NEW MATTER REJECTION, is withdrawn in view of Applicants amendments.

Rejection Maintained:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 33 and 35-36 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of

experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the nature of the invention, (2) the relative skill of those in the art, (3) the breadth of the claims, (4) the amount or direction or guidance presented, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the state of the prior art, and (8) the predictability or unpredictability of the art.

Although the quantity of experimentation alone is not dispositive in a determination of whether the required experimentation is undue, this factor does play a central role. For example, a very limited quantity of experimentation may be undue in a fledgling art that is unpredictable where no guidance or working examples are provided in the specification and prior art, whereas the same amount of experimentation may not be undue when viewed in light of some guidance or a working example or the experimentation required is in a predictable established art. Conversely, a large quantity of experimentation would require a correspondingly greater quantum of guidance, predictability and skill in the art to overcome classification as undue experimentation. In Wands, the determination that undue experimentation was not required to make the claimed invention was based primarily on the nature of the art, and the probability that the required experimentation would result in successfully obtaining the claimed invention. (Wands, 8 USPQ2d 1406) Thus, a combination of factors which, when viewed together, would provide an artisan of ordinary skill in the art with an expectation of successfully obtaining the claimed invention with additional experimentation would preclude the classification of that experimentation as undue. A combination of Wands factors, which provide a very low likelihood of successfully obtaining the claimed invention with additional experimentation, however, would render the additional experimentation undue.

The nature of the invention

The claims are drawn to a method of screening for an agent which modulates the function of a protein comprising the amino aid sequence of SEQ ID NO: 5. The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Level of skill in the art

The level of skill in the art is deemed to be high, generally that of a master's level student or Ph.D.

The breadth of the claims

Applicants broadly claim method of screening for an agent which modulates the function of a protein comprising the amino acids sequence of SEQ ID NO: 5, comprising incubating a mixture comprising an isolated protein comprising the amino acid sequence of SEQ ID NO: 4 with an altered PYI motif at residues 564-566; the sequence of SEQ ID NO: 2 or a fragment thereof comprising SEQ ID NO: 5 or SEQ ID NO: 6; and a candidate agent under conditions whereby, but for the presence of said agent, said isolated protein mediates VHL-dependent degradation or physically interacts with VHL at a reference affinity; and detecting the binding affinity of said protein to SEQ I DNO: 2 to determine an agent based affinity, wherein a difference between said reference affinity and said agent-based affinity indicates that said agent modulates the functional activity of said isolated protein to said sequence of SEQ ID NO: 2 or a fragment thereof comprising SEQ IDNO: 5 or SEQ ID NO: 6. Thus, the claims imply that there is a direct relationship between the protein comprising an amino acid sequence of SEQ ID NO: 5 and an isolated protein comprising the amino acid sequence of SEQ ID NO: 4 with an altered PYI motif at resides 564 to 566, e.g., the isolated protein mediates VHL-degradation or physically interacts with VHL at a reference affinity.

Guidance in the specification and Working Examples

The specification teaches that both the HIF-1 alpha (SEQ ID NO: 4) interaction domain and the elongin C binding domain of VHL are necessary to mediate degradation of HIF-1, and that regulation of HIF-1 alpha may be involved in the tumor suppressor function of VHL (paragraph 00101). In particular, the specification teaches that the PYI motif of HIF-1 alpha is critical for interaction with VHL and any amino acid substitution that changes positions 564-566, e.g., PYI, will effectively abrogate this interaction with the VHL protein (paragraphs 0111 and 0112). For example, the specification teaches that amino acid substitutions at Y565 or I566 can abrogate

interaction with VHL (paragraphs 0113-0115). Thus, the specification appears to set forth that alteration of the PYI motif abrogates any interaction with VHL; and as such, appears to be in direct contrast with the claimed invention with implies that that said isolated protein comprising the amino acid sequence of SEQ ID NO: 4 with an altered PYI motif at resides 564-566 mediates VHL dependent degradation or physically interacts with VHL at a reference affinity. While it is understood that the absence of working examples should never be the sole reason for rejecting a claim as being broader than an enabling disclosure, the criticality of working examples in the instant case is required for practice of the claimed invention because it can not be determined how a compound can be identified if the reference affinity, e.g. VHL interaction with HIF, is essentially none.

Quantity of experimentation

The quantity of experimentation is extremely large given the unpredictability associated with screening for agents which modulate the function of a protein comprising the amino acid sequence of SEQ ID NO: 5 by detecting the difference between the binding affinity of an isolated protein comprising the amino acid sequence of SEQ ID NO: 4 with an altered PYI motif to VHL without a candidate agent compared to the binding affinity of an isolated protein comprising the amino acid sequence of SEQ ID NO: 4 with an altered PYI motif to VHL in the presence of a candidate agent because as noted through out the specification, alteration of the PYI motif abrogates the interaction with VHL.

The state of the prior art

As reflected in the specification, the state of the art at the time of filing was such that one of skill could recognize that the minimal N-terminal transactivation domain of HIF-1a is a target for ubiquitination and proteosomal degradation by VHL. For example, Cockman et al. (JBC 2000; 275: 25733-25741) teach that amino acids 549-582 of HIF-1a are sufficient for pVHL interaction (page 25739, 2nd column, 1st full paragraph). Similarly, Tanimoto et al. (EMBO 2000; 19: 4298-4309, IDS) teach that the N-terminal transactivation domain (N-TAD) of HIF-1a is a sequence motif of 19 amino acid residues comprising a highly conserved core motif of PYI which is critical for interaction with VHL (page 4303, 1st column, 1st full paragraph). In particular, Tanimoto et al. teach that

substitution of the central PYI triplet with aspartic acid totally abolishes interaction with VHL and the N-TAD (page 4303, 1st column, 1st full paragraph). Thus, while considerable research has gone into to studying HIF-1a binding and ubiquitination by VHL, one of skill in the art would recognize that the PYI triplet of HIF-1a is critical for its interaction with VHL.

Conclusion

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the lack of guidance provided in the specification and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as written.

In response to this rejection, Applicants assert that claim 33 recites a negative control assay for testing a substance that has shown to bind to normal HIF protein comprising a HIF protein comprising an altered PYI motif at residues 564-566 substituted for a normal HIF protein. Moreover, Applicants contend that in its basic form, the claimed invention is an assay comprising an incubating step and a detecting step. For example, Applicants assert that the assay comprises mixing HIF or a fragment of HIF comprising the normal PYI motif with a test substance that can hamper the interaction between the HIF and the VHL protein or a fragment thereof, wherein the HIF protein would not be degraded in the presence of a hampering substance. In contrast, Applicants assert that the modified PYI motif according to the present invention brings about a lower affinity between the HIF protein and VHL, wherein the HIF protein is degraded by VHL to a less degree compared to the native sequence. In addition, Applicants assert that the references cited by the Examiner were both published after the priority date of the present application and therefore, can not be considered prior art.

These arguments have been carefully considered, but are not found persuasive.

First, the Examiner recognizes that the claims encompass, as noted by Applicants, a method of screening for an agent which modulates the function of a protein comprising the amino acids sequence of SEQ ID NO: 5, comprising incubating a mixture comprising an isolated protein

comprising the amino acid sequence of SEQ ID NO: 4 with an altered PYI motif at residues 564-566; the sequence of SEQ ID NO: 2 or a fragment thereof comprising SEQ ID NO: 5 or SEQ ID NO: 6; and a candidate agent under conditions whereby, but for the presence of said agent, said isolated protein mediates VHL-dependent degradation or physically interacts with VHL at a reference affinity; and detecting the binding affinity of said protein to SEQ I DNO: 2 to determine an agent based affinity, wherein a difference between said reference affinity and said agent-based affinity indicates that said agent modulates the functional activity of said isolated protein to said sequence of SEQ ID NO: 2 or a fragment thereof comprising SEQ IDNO: 5 or SEQ ID NO: 6. As such, the claims do not appear to require normal HIF protein comprising a HIF protein with an unaltered PYI motif as asserted by Applicants. As noted above, the claims appear to suggest that there is a direct relationship between the protein comprising an amino acid sequence of SEQ ID NO: 5 and an isolated protein comprising the amino acid sequence of SEQ ID NO: 4 with an altered PYI motif at resides 564 to 566, e.g., the isolated protein mediates VHL-degradation or physically interacts with VHL at a reference affinity. However, the specification appears to set forth that alteration of the PYI motif abrogates any interaction with VHL. As such, it is unclear how one of ordinary skill in the art could use the claimed invention with any predictability. Regarding Applicants contention that the references cited by the Examiner are not prior art, the Examiner acknowledges and does not dispute Applicants assertions that both the references were published after the earliest priority date of the instant application. However, the Examiner recognizes that the references were not cited as prior art references, but instead represent the state of the art. As such, these arguments are considered moot.

Therefore, No claim is allowed.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be

calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BRANDON J. FETTEROLF whose telephone number is (571)272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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